# 16

**Docket No.: PF-0475-2 DIV**

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1644

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By: _____ Printed: Lisa McDill



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: Lal et al.

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| Title: | HUMAN SHORT-CHAIN DEHYDROGENASE | | |
| Serial No.: | 10/006,163 | Filing Date: | December 4, 2001 |
| Examiner: | Huynh, P.N. | Group Art Unit: | 1644 |

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## REPLY BRIEF ON APPEAL

Sir:

## I. INTRODUCTION

This is Appellants' Reply Brief on Appeal (submitted in triplicate) in response to the Examiner's Answer dated September 23, 2003 ("the Examiner's Answer") in the above-identified application (the Lal '163 application).

In the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of claims 11, 36, and 37, on appeal, under 35 U.S.C. § 102(b) on the grounds that the claimed antibodies are allegedly anticipated by Verwoert et al. (J. Bacteriol., 1992, 174:2851-2857),

(2) maintained the rejection of claims 11, 31, 42, and 43, on appeal, under 35 U.S.C. § 103(a) on the grounds that the claimed antibodies are obvious over Verwoert et al. (J. Bacteriol., 1992, 174:2851-2857) in view of Queen et al. (U.S. Patent No. 6,180,370 B1),

(3) maintained the rejection of claims 11 and 31, on appeal, under 35 U.S.C. § 103(a) on the grounds that the claimed antibodies are obvious over Verwoert et al. (J. Bacteriol., 1992, 174:2851-2857) in view of Ladner et al. (U.S. Patent No. 4,946,778),

(4) maintained the rejection of claims 11, 31, 32, and 34, on appeal, under 35 U.S.C. § 103(a) on the grounds that the claimed antibodies are obvious over Verwoert et al. (J. Bacteriol., 1992, 174:2851-2857) in view of Harlow et al. (in Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pages 319-356 and 626-629),

(5) maintained the rejection of claims 11 and 38-41, on appeal, under 35 U.S.C. § 103(a) on the grounds that the claimed antibodies are obvious over Verwoert et al. (J. Bacteriol., 1992, 174:2851-2857) in view of Harlow et al. (in Antibodies a Laboratory Manual, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pages 139-149),

(6) maintained the rejection of claims 11, 31, 32, 34, 36-43, and 58, on appeal, under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed antibodies, and

(7) maintained the rejection of claims 11, 31, 32, 34, 36-43, and 58, on appeal, under 35 U.S.C. § 112, first paragraph, for alleged lack of written description/possession of the claimed antibodies.

## II. ISSUE 1 -- ANTICIPATION REJECTIONS

In maintaining the anticipation rejection of claims 11, 36, and 37, the Examiner insists that "in the absence of specific teachings that specific binding is not equate with cross-reactivity, the claimed antibody appears to be the same as that of the reference antibody" (Examiner's Answer, page 14).

However, the Examiner has not met the burden of showing that the antibody taught by Verwoert et al. (J. Bacteriol., 1992, 174:2851-2857) is the same as the claimed antibody.

The basis of this rejection is that "Verwoert *et al* teach an antibody that specifically binds to an epitope, which is a fragment such as VTGASRGIGRGIA of a polypeptide such as Malonyl coenzyme A-Acyl carrier protein transacylase that has a stretch of contiguous amino acid residues (epitope) *identical* to the claimed SEQ ID NO:1" (Examiner's Answer, page 14; emphasis in original). However, to support an anticipation rejection, there is a burden on the Examiner to provide convincing proof that the references teach the claimed invention. In this case, the Examiner has not met this burden. The Examiner has **not** provided convincing evidence that the antibody taught by Verwoert et al. is the same as the antibody recited by the claims. Instead, the Examiner states that "the claimed antibody appears to be the same as that of the reference antibody," and allege that this appearance of sameness shifts the burden of proof to the Appellants to "show that the prior art antibody is different from the claimed antibody" (Examiner's Answer, page 14). This is improper.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102(b), "the reference must teach every aspect of the claimed invention either explicitly or implicitly." M.P.E.P. § 706.02. With respect to the instant anticipation rejections, the relevant section of claim 11 recites "an antibody which specifically binds to a polypeptide comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1, and wherein the antibody specifically binds to an epitope of the fragment." Although Verwoert et al. teach antibodies which bind to arbitrary and unspecified fragments of malonyl coenzyme A-acyl carrier protein transacylase, this references does not explicitly teach an antibody which binds to the 13 contiguous amino acids VTGASRGIGRGIA. This is because the Verwoert reference teaches the 12 contiguous amino acids VTGASRGIG**RAI** (see, e.g., the last full line of the sequence translation in Figure 2 on page 2853 of Verwoert et al.), which is not identical to the 13 contiguous amino acids VTGASRGIG**RGIA** found at residues 12-24 of SEQ ID NO:1.

Furthermore, although Verwoert et al. teach an antibody which may bind to an epitope consisting of the 12 contiguous amino acids VTGASRGIGRAI (which is not the 13 contiguous amino

acids VTGASRGIGRGIA of SEQ ID NO:1), such an antibody is not the same as an antibody that specifically binds to a polypeptide comprising "at least **15** contiguous amino acid residues of SEQ ID NO:1." Thus, since Verwoert et al. do not explicitly teach the claimed antibody, the Verwoert reference must teach the claimed antibody implicitly if the reference is to be used as the basis for a rejection under 35 U.S.C. § 102(b). In effect, the Examiner has asserted that the claimed antibody is inherent in the teachings of Verwoert et al. However, the Examiner has not provided any convincing proof that this is in fact the case.

The Examiner must provide a rationale or evidence tending to show that the properties of the claimed subject matter are inherent in the references used in an anticipation rejection. "The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)" M.P.E.P. § 2112 (emphasis in original). " '[T]he examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art.' *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)" *Id.* (emphasis in original).

Verwoert et al. teach an antibody that binds to arbitrary and unspecified fragments of malonyl coenzyme A-acyl carrier protein transacylase. Based on alleged sequence identity between this enzyme and SEQ ID NO:1, the Examiner asserts that Verwoert et al. teach an antibody which binds to an epitope consisting of the 13 contiguous amino acids VTGASRGIGRGIA (even though Verwoert et al. do not teach this amino acid sequence). However, an antibody that specifically binds to at least 15 contiguous amino acid residues of SEQ ID NO:1 **does not** "necessarily flow" from the teachings of the Verwoert reference. For example, an antibody that binds to arbitrary and unspecified fragments of the malonyl coenzyme A-acyl carrier protein transacylase, as taught by Verwoert et al., would not necessarily bind to an epitope of SEQ ID NO:1 consisting of at least 15 contiguous amino acid residues of SEQ ID NO:1, even if that epitope included the 13 contiguous amino acid residues VTGASRGIGRGIA. This is because there is no indication that the antibody taught by Verwoert et al. binds to the 13 contiguous amino acid residues VTGASRGIGRGIA. In addition, even if the antibody of Verwoert et al. did bind to the 13 contiguous amino acid residues VTGASRGIGRGIA (Appellants

maintain that there is no indication that it so binds), it would not necessarily bind to at least 15 contiguous amino acid residues of SEQ ID NO:1. The claimed antibody is not an inherent property that "**necessarily** flows" from the teachings of Verwoert et al., and therefore Verwoert et al. does not anticipate the claimed antibodies. Because there is the possibility that Verwoert et al. does not teach the claimed antibody, the Examiner has not met the burden to make a *prima facie* showing of anticipation.

The Examiner asserts that the antibody of Verwoert et al. is necessarily the same as the claimed antibody by stating that "Appellants state on the record that the reference antibodies taught by Verwoert et al could possibly bind to a polypeptide comprising SEQ ID NO:1 or fragments or variants thereof" (Examiner's Answer, page 14). However, the Examiner continues to ignore that even if the antibody of Verwoert et al. could possibly bind to a fragment of SEQ ID NO:1 containing the 13 contiguous amino acid residues VTGASRGIGRGIA, this binding would not be **specific**. The antibodies recited by the claims **specifically** bind to "a polypeptide comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1, and wherein the antibody specifically binds to an epitope of the fragment." The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims.

The Examiner asserts that "[s]ince the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody" (Examiner's Answer, page 14). However, the Examiner has not made a *prima facie* showing of anticipation. To meet the legal standard for a *prima facie* showing of anticipation, the Examiner would need to show that a reference antibody is necessarily the same as the claimed antibody. Since the antibody taught by Verwoert et al. could be an antibody which is not the same as the claimed antibody, the claimed antibody is not **necessarily** the same as the antibody taught by the cited reference. Until a *prima facie* case of anticipation has been made, it is improper to shift the burden of proof to the Appellants.

The Examiner has improperly rejected claims 11, 36, and 37 based on alleged anticipation by Verwoert et al. because he has not made a *prima facie* showing by providing convincing evidence that this reference anticipates the claimed antibodies. For at least the above reasons, this rejection should be overturned.

## III. ISSUES 2-5 -- OBVIOUSNESS REJECTIONS

All of the obviousness rejections under 35 U.S.C. § 103(a) are based on the allegation that the antibodies taught by Verwoert et al. anticipate antibodies which specifically bind to "a polypeptide comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1, and wherein the antibody specifically binds to an epitope of the fragment." As discussed above under Issue 1 (e.g., in § II), the Verwoert et al. reference does not anticipate the antibodies recited by the claims because the antibodies disclosed by Verwoert et al. are not **necessarily** the same as the claimed antibodies. "The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)" M.P.E.P. § 2112 (emphasis in original). " '[T]he examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art.' *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)" *Id.* (emphasis in original). Therefore, the Examiner has not made a *prima facie* case that the claims are obvious.

Furthermore, the claims recite antibodies which **specifically** bind to "a polypeptide comprising an immunogenic fragment of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, wherein said fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1, and wherein the antibody specifically binds to an epitope of the fragment." The antibodies taught by Verwoert et al. are excluded from the claimed antibodies because they bind to polypeptides other than those recited in the claims. Therefore, a *prima facie* case that the claims are obvious is not supported.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art" and "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." M.P.E.P. § 2143.03. In maintaining the obviousness rejections under 35 U.S.C. § 103, the Examiner continues to ignore the fact that the characteristics of the antibodies recited in the claims do not **necessarily flow** from the alleged prior art products of Verwoert et al., as discussed above under Issue 1 (e.g., in § II). Therefore, Verwoert et al. do not teach the antibodies recited by the claims. The Examiner has not convincingly shown that all of the elements of the claimed subject matter are taught by the cited references, and has not convincingly shown how the references could be modified to arrive at the claimed subject matter. Therefore, the Examiner has not made a *prima facie* case for obviousness.

## IV. ISSUE 6 -- ENABLEMENT REJECTIONS

In maintaining the rejection of the claimed antibodies for alleged lack of enablement, the Examiner continues to focus on a misguided requirement for knowledge of the precise sequences of the polypeptides specifically bound by the claimed antibodies. The Examiner asserts that "[o]ther than the antibody that binds specifically to the specific polypeptide of SEQ ID NO:1 or 3, the specification does not teach how to make, much less how to use any antibody that binds to any undisclosed epitope of any polypeptide at least 90% identical to the amino acid sequence of SEQ ID NO:1 which include numerous changes and variation such as substitution, insertion and deletion" (Examiner's Answer, page 24). However, the Examiner completely ignores that the specification discloses methods to make and use antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence. Furthermore, such methods to make and use any antibody are known in the art and can be routinely carried out by a skilled artisan without undue experimentation.

The Examiner further asserts that "[t]he specification does not provide guidance as to which one or more amino acids of SEQ ID NO:1 is altered such as substitution, insertion and deletion and whether the resulting polypeptide variant retains its three dimensional structure and has biological function, much less about whether it retains antibody binding to said polypeptide variant" (Examiner's Answer, page 24). For the purposes of the enablement requirement, it is not necessary that a

polypeptide variant retains the three dimensional structure of its parent polypeptide, or that it has any biological function, for one of skill in the art to be able to make and use an antibody that specifically binds to that polypeptide variant. A skilled artisan would be able to make and use an antibody which, for example, specifically bound to a polypeptide variant having no known biological function, without undue experimentation.

On page 25 of the Examiner's Answer, the Examiner states that "Applicants state on record . . . that antibodies which specifically to a polypeptide can be made as long as that polypeptide or fragments thereof, are available. However, the amino acid sequence of a polypeptide that is 90% identical to SEQ ID NO:1 to which the claimed antibody binds is not available." Contrary to the Examiner's assertions, the recited polypeptide variants are routinely available. Note that claim 11, for example, recites not only that the recited polypeptide variants are at least 90% identical to SEQ ID NO:1, but also that they have "**a naturally occurring amino acid sequence**." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of HSCD) and SEQ ID NO:2 (the polynucleotide sequence encoding HSCD), one of skill in the art would be able to routinely obtain "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1."

For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application. See, e.g., page 16, lines 9-12 and 24-28; page 25, lines 12-24; page 36, line25 to page 37, line 13; and Example VI at pages 47-48. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides

of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims using conventional techniques of recombinant protein production. In addition, the specification discloses a specific assay for measuring the CoA dehydrogenase activity of the recited HSCD variants (e.g., at page 50, line 21 to page 51, line 2). Therefore, contrary to the Examiner's assertions, the recited polypeptides to which the claimed antibodies specifically bind would be routinely available to a skilled artisan, without undue experimentation.

The Examiner continues to insist that the use of the term "comprising" precludes enablement of the claimed antibodies because "one of skill in the art could not predict which undisclosed antibody would bind specifically to any undisclosed polypeptide such as fusion protein that comprises additional undisclosed amino acid residues in addition to SEQ ID NO:1 and whether antibody still binds to said undisclosed protein in the absence of guidance as to the binding specificity of the claimed antibody" (Examiner's Answer, page 26). However, the Examiner ignores that there is no requirement for explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter. The claimed antibodies specifically bind to the recited epitopes. Therefore, it is irrelevant whether the specification enables antibodies which specifically bind to additional amino acid residues at "either or both ends" of the recited polypeptides, variants, and fragments of SEQ ID NO:1.

Furthermore, the Examiner asserts that "there is insufficient guidance as to the structure of the polypeptide as set forth in claim 11c because of the additional undisclosed amino acid at either or both ends of the immunogenic fragment and whether the antibody generated from any undisclosed fragment having extra undisclosed amino acids would bind specifically to any epitope of the fragment of SEQ ID NO:1" (Examiner's Answer, page 28). It is irrelevant whether the claimed antibodies are "generated from any undisclosed fragment" because the claimed antibodies would specifically bind to the recited epitopes regardless of how they were generated. There is no question of whether the claimed antibodies would specifically bind to the recited epitopes because the claim language defines the claimed antibodies such that they do specifically bind to the recited epitopes. Moreover, one of skill in the art would be able to routinely determine whether any particular antibody specifically bound to any particular epitope by, for example, using screening methods well known in the art (Specification, e.g., at

page 29, line 24 to page 30, line 1). Therefore, the explicit disclosure of amino acid residues that may or may not be at "either or both ends" of the recited polypeptides, variants, and fragments of SEQ ID NO:1 is not necessary for enablement of the claimed antibodies.

The Examiner continues this argument by citing Kuby et al. (Immunology, Second edition, 1994, W.H. Freeman and Company, New York, NY, pages 86-96). The Examiner states that "**antibody specificity** generated from a fragment differs from antibody specificity directed against the native full-length polypeptide, let alone any fusion protein" (Examiner's Answer, page 28; emphasis in original). Again, there is no question of whether the claimed antibodies would specifically bind to the recited epitopes because the claim language defines the claimed antibodies such that they do specifically bind to the recited epitopes. The Examiner's citation of Kuby et al. is irrelevant because the Examiner's argument ignores the plain language of the claims.

The Examiner takes issue with the Appellants' comments regarding Ngo et al. (in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Birkhauser Boston, pages 492-495) and Abaza et al. (J. Prot. Chem., 1992, 11:433-444). The Examiner asserts that "one of ordinary skill in the art would not be able to determine, without undue experimentation, the positions in the SEQ ID NO:1 polypeptide which are tolerant to change and the nature and extent of changes that can be made in these positions and the claimed antibody still binds" (Examiner's Answer, page 29). Once again, it would be routine to determine whether any particular antibody specifically binds to the recited polypeptides. One of skill in the art would be able to routinely determine whether any particular antibody specifically bound to any particular polypeptide by, for example, using screening methods well known in the art (Specification, e.g., at page 29, line 24 to page 30, line 1).

With respect to the Abaza reference, the Examiner contends that "an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity of the claimed variant polypeptide and fragments of SEQ ID NO:1" (Examiner's Answer, page 30). However, whether or not the Examiner's contention is true, it has no bearing on whether one of skill in the art could make and/or use the claimed antibodies, without undue experimentation. Even if a polypeptide variant has an amino acid substitution which drastically affects

the reactivity of a monoclonal antibody which specifically binds to the parent polypeptide, a skilled artisan would still known how to use that polypeptide variant to make antibodies which specifically bind to the polypeptide variant. In addition, one of skill in the art would know how to use such antibodies to purify and/or detect the polypeptide variant. Therefore, the claimed antibodies meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner continues to refuse to accept a constructive reduction to practice for the claimed invention, stating that "[u]ntil the time when such variants and fragments of SEQ ID NO:1 are identified, then one skill in the art can make antibodies against those variants and fragments of SEQ ID NO:1" (Examiner's Answer, page 30). Not so. The amino acid sequence of the polypeptide of SEQ ID NO:1 has been explicitly disclosed in the specification (see, e.g., the Sequence Listing and Figures 1A, 1B, 1C, 1D, and 2), and it would be routine for a skilled artisan to obtain the recited polypeptide variants and fragments of SEQ ID NO:1. Methods of making and using antibodies which specifically bind to polypeptides (including polypeptides based on the SEQ ID NO:1 polypeptide) have also been disclosed in the specification (e.g., at page 28, line 6 to page 29, line 23; and page 51, line 4 to page 52, line 2). In conjunction with the disclosure in the specification and the knowledge in the art at the time the application was filed, a skilled artisan would know how to make and use the claimed antibodies. Thus, the constructive reduction to practice of the claimed antibodies more than adequately provides enablement for the claimed invention.

The Examiner asserts that "[t]he intended use for the composition comprising the claimed antibody such as monoclonal, chimeric, single chain, Fab fragment, (Fab')2 fragment and humanized antibody and an acceptable excipient as discloses on page 32, line 14 of the specification is for in vivo therapy" (Examiner's Answer, page 31). While the specification discloses that "[a]n additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects . . ." (page 32, lines 13-15), this does not limit the use of the recited compositions to *in vivo* therapeutic use. *In vivo* therapeutic use is only one possible use of the recited compositions. For example, compositions

comprising the claimed antibodies can be used to detect and/or purify polypeptides which are specifically bound by the claimed antibodies.

All that is required to meet the enablement requirement of 35 U.S.C. § 112, first paragraph, is that the specification must enable one of skill in the art to make and use the claimed invention. As cited in the Brief on Appeal, *In re Marzocchi*, 169 USPQ 367 (CCPA 1971) states that "[h]ow such a teaching [of objective enablement] is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." In the subject application, the claimed antibodies are enabled because the limitations recited in the claims limit the claimed subject matter to antibodies that a skilled artisan could make and use based on the disclosure of the specification and the state of the art at the time the application was filed. For example, a skilled artisan would know how to make and use the recited antibodies which specifically bind to polypeptides comprising "a naturally occurring amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1, wherein said polypeptide has CoA dehydrogenase activity" because the recitation of "naturally occurring amino acid sequence" and "has CoA dehydrogenase activity" restricts the recited polypeptides to those that have been determined to be useful through the process of natural selection.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

## V. ISSUE 7 -- WRITTEN DESCRIPTION REJECTIONS

### A. Overview of Written Description Rejections

Nowhere in the Examiner's Answer does the Examiner offer any evidence that one of ordinary skill in the art would not have understood, from the disclosure in the specification, along with "[w]hat is conventional or well known to one of ordinary skill in the art," that Appellants were in possession of the claimed antibodies which specifically bind to the recited epitopes. The Examiner instead states that "appellants have not teach any naturally occurring variant that is at least 90% identical to SEQ ID NO:1 neither did appellant teach any fragments of SEQ ID NO:1, see sequence listing in particular, much less

about the binding specificity of claimed antibody or epitope of any polypeptide at least 90% identical to SEQ ID NO:1 or polypeptide comprising immunogenic fragment of SEQ ID NO:1 to which the claimed antibody binds" (Examiner's Answer, page 32).

The Examiner's position is contrary to the Patent and Trademark Office's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. **What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.** [footnotes omitted; emphasis added]

Here, there simply is no requirement that the claims recite the sequences of particular variants and fragments because the claims already provide sufficient structural definition of the claimed subject matter. That is, the claimed antibodies specifically bind to polypeptides, variants, and fragments which are defined in terms of SEQ ID NO:1. Because the recited polypeptides, variants, and fragments are defined in terms of SEQ ID NO:1, the precise chemical structure of every polypeptide, variant, and fragment recited by the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention.

## B. Responses to Specific Arguments by the Examiner

1. On page 32 of the Examiner's Answer, the Examiner continues to insist that the use of the term "comprising" precludes an adequate written description of the claimed antibodies because "[t]here is inadequate written description about the undisclosed amino acids at either or both ends of the fragment." However, the Examiner has not addressed any of the arguments previously presented by the Appellants (e.g., on pages 17-18 of the Brief on Appeal of June 30, 2003). The Examiner's

repetition of the original grounds for rejection in no way demonstrates that there is an inadequate written description of the claimed antibodies which specifically bind to polypeptides "comprising" polypeptides, variants, and fragments of SEQ ID NO:1. The Examiner ignores that there is no requirement for explicit disclosure of every possible element which could be a part of, but is not essential to, the claimed subject matter. The Examiner also ignores that the claims recite antibodies which specifically bind to epitopes on the recited polypeptides, variants, and fragments of SEQ ID NO:1.

2. On page 34 of the Examiner's Answer, the Examiner asserts that "[t]he description of antibody that binds to a polypeptide of SEQ ID NO:1 in the specification of the instant application is not a representative number of embodiments to support the description of an entire genus of functionally equivalent polypeptides which incorporate all mutants, derivatives, variants and fragments having at least 90% identity to the amino acid sequences of SEQ ID NO:1 to which the antibody binds." The Examiner is incorrect in asserting that all of the recited polypeptides are "functionally equivalent." For example, while the recited variant polypeptides have "CoA dehydrogenase activity," the recited polypeptide fragments are not limited to only those fragments having CoA dehydrogenase activity.

Furthermore, the Examiner errs in asserting that the genus of polypeptides specifically bound by the claimed antibodies incorporates "**all** mutants, derivatives, variants, and fragments." For example, the recited variant polypeptides comprise "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said polypeptide has CoA dehydrogenase activity." This genus of variant polypeptides is not the same as the genus encompassing all polypeptides "having at least 90% identity to the amino acid sequence of SEQ ID NO:1."

3. The Examiner asserts on page 34 of the Examiner's Answer that "Appellants have not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of polypeptides to which the claimed antibody binds as recited in the claims. The specification and claims do not indicate which characteristics are shared by members of the genus." Not so. Appellants have provided at least one structural feature, the explicitly disclosed amino acid sequence of SEQ ID NO:1, which relates the members of the genus of claimed antibodies. Given SEQ ID NO:1, one of ordinary skill in the art would recognize polypeptides which are variants comprising an amino acid sequence at least 90% identical to SEQ ID NO:1 and having CoA

dehydrogenase activity, or which are fragments comprising at least 15 contiguous amino acid residues of SEQ ID NO:1. The description of the recited polypeptides in terms of the chemical structure of SEQ ID NO:1 provides an adequate written description for the claimed antibodies which specifically bind to these polypeptides.

4. On page 34 of the Examiner's Answer, the Examiner insists that the genus of claimed antibodies is "highly variant," stating that "[t]he scope of the claims includes numerous structural variants and the genus is highly variant because a significant number of structural differences between genus members are permitted" (Examiner's Answer, page 34). However, the Examiner has provided no evidence to support these assertions. In contrast, Appellants have provided objective evidence (e.g., the Brenner et al. reference (Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078) ) to demonstrate that the recited genus of polypeptide variants is not "highly variant." The objective evidence of record (e.g., the Brenner reference) indicates that a skilled artisan would consider the genus of polypeptides which are at least 90% identical to SEQ ID NO:1 to not be "highly variant." Therefore, a skilled artisan would consider the genus of antibodies which specifically bind to these polypeptides to also not be "highly variant."

5. The Examiner asserts that "[t]he specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants" (Examiner's Answer, page 35). However, the Examiner ignores the fact that the general discussion of making and screening for variants was presented in the specification to demonstrate the state of the art at the time the application was filed. The written description inquiry must consider not only what is disclosed in the specification, but also "[w]hat is conventional or well known to one of ordinary skill in the art." A skilled artisan, taking into account the disclosure in the specification (e.g., the explicit recitation of the chemical structure of SEQ ID NO:1) and the state of the art, would reasonably conclude that the Appellants had possession of the claimed antibodies at the time the application was filed.

C. **Summary**

The Examiner has asserted that the sequence of each of the recited polypeptide variants and fragments must be provided in order for there to be an adequate written description of the claimed genus of antibodies. However, this is not true. The Patent Office guidelines state that an adequate written description can be provided by "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). Therefore, there is no absolute requirement to provide the sequence of every polypeptide which is specifically bound by the claimed antibodies. The claimed antibodies which specifically bind the recited variants and fragments of the SEQ ID NO:1 polypeptide have been described by chemical structure (e.g., relation of the recited polypeptide variants and fragments to SEQ ID NO:1), physical properties (e.g., occurrence in nature of the recited polypeptide variants), and chemical properties (e.g., possession of CoA dehydrogenase activity by the recited polypeptide variants; specific binding of the claimed antibodies to the recited polypeptide variants and fragments). Therefore, the written description requirement has been met.

For at least the above reasons and the reasons presented in the Brief on Appeal, reversal of this rejection is requested.

## VI. CONCLUSION

For all the foregoing reasons and the reasons stated in the Appellants' Supplemental Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

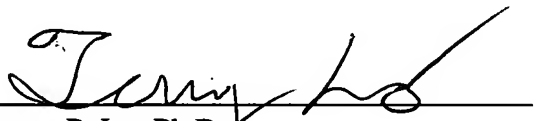
If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

**This form is enclosed in triplicate.**

Respectfully submitted,

INCYTE CORPORATION

Date: November 19, 2003



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